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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,689	12/17/2004	Antonio Guarna	50294/014001	5376

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EXAMINER	
RAMACHANDRAN, UMAMAHESWARI	
ART UNIT	PAPER NUMBER
1617	

NOTIFICATION DATE	DELIVERY MODE
12/11/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/518,689	GUARNA ET AL.	
	Examiner	Art Unit	
	UMAMAHESWARI RAMACHANDRAN	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-25,27-40 and 42* is/are pending in the application.

4a) Of the above claim(s) *27-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-25, 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner notes the receipt of the amendments and remarks received in the office on 11/29/2007 amending claims 22, 42. Claims 1-21, 41,26 are cancelled and claims 27-40 are withdrawn from consideration. Claims 22-25, 42 are pending and are being examined on the merits herein.

Response to Remarks

Applicants' arguments regarding the rejection of claims 22-26, 42 under U.S.C 103 for obviousness over Guarna (1999), the rejection of claims 22-25, 42 under 35 U.S.C. 103(a) as being unpatentable over Cini et al (Eur J of Org Chem, March 2002, 873-880) has been fully considered and found not persuasive and the response to arguments is provided below. Applicants' amendments necessitated the modified rejections presented in this action. Accordingly, the action is made Final.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 22-25, 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guarna et al. (Applicant-cited reference on IDS: Guarna et al. J. *Org. Chem.* 1999, *64,* 7347-7364.).

Guarna et al. teach compounds within the scope of the instant genus of compounds comprising the 3-aza-bicyclo[3.2.1]octane core, as well as specific compounds defined in the instant claim 25. For example, Guarna et al. teach compound 192 of the instant claim 25, which is the compound of the instant formula (I) wherein X, Y, and Z are O, R1, R4, and R5 are H, R2 is (S)-Me (C1 alkyl), R3 is C1 arylalkyl, and R6 is (R)-C(O)OR, wherein R is C1 alkyl (see compound 12 on p. 7353). Guarna et al. teach a general strategy for preparing all of the individual stereoisomers of the compounds comprising the 3-aza-bicyclo[3.2.1]octane core (see Chart 1 on p. 7349). Guarna et al. teach, "Peptide isosteres are compounds that can replace one or more amino acids in a bioactive peptide leading to modified structures possibly displaying more favorable pharmacological properties than the prototype. In several cases, the modified peptide shows a higher metabolic stability, better bioavailability, and properties of peptide isosteres that would achieve these desired pharmacological properties. Guarna et al. state, "We have envisioned that some of...these features could be found in the bicyclic structure based upon 3-aza-6,8-dioxabicyclo[3.2.1]octane-7-carboxylic acid skeleton". Thus, Guarna et al. suggest the pharmaceutical utility of compounds comprising the 3-aza-bicyclo[3.2.1]octane core In addition, the reference teach that BTAa(O) compounds, (some of the compounds that are instantly claimed)

are corresponding amide precursors of BTAs (dipeptide isoteres) (p 7348, col. 1, lines 1-4), and teach the transformation of BTAa(O) to BTAa compounds (p 7353, scheme 5, compounds 16-21). Hence the reference teach the utility of BTAa(O) compounds as the precursor of dipeptide isoteres that can replace one or one or more amino acids in a bioactive peptide leading to modified structures possibly displaying more favorable pharmacological properties than the prototype. The reference further teach other BTAa(O) compounds such as wherein X, Y, and Z are O, R1, R4, and R5 are H, R2 is Me (exo, endo) (C1 alkyl), R3 is C1arylalkyl, and R6 is (R)-C(O)OR (exo) (see compounds 6 and 7 of table 1, p 7349). This teaches the compounds 5 and 6 of claim 25 . The reference teaches BTAa(O) compounds in Table 1, (see compounds 1, 4, 5, 10 and 11) compounds 191-192, 196-199 claimed in claim 42. .

Guarna et al. do not explicitly teach the instant compounds 193-195 as defined in claim 25, which are stereoisomers of compound 192 of the instant claim 25. Guarna et al. do not teach preparation of pharmaceutical compositions comprising the herein-claimed compounds comprising the 3-aza-bicyclo[3.2.1]octane core.

For the reasons discussed above, the herein-claimed stereoisomers of the compounds disclosed by Guarna et al. are prima facie obvious, particularly considering that Guarna et al. teach a general strategy for preparing all of the possible stereoisomers. For the reasons discussed above, the herein-claimed adjacent homologs and homologous series are prima facie obvious. Because Guarna et al. suggest the pharmaceutical utility of the herein-claimed compounds comprising the 3-aza-bicyclo[3.2.1]octane core, it would have been obvious to the person of ordinary skill

in the art to formulate the compounds with pharmaceutically acceptable excipients to arrive at the instantly claimed inventions.

The person of ordinary skill in the art would have been motivated to formulate the compounds of Guarna et al. with pharmaceutically acceptable excipients as a pharmaceutical composition because Guarna et al. teach the compounds and suggest the pharmaceutical utility of the herein-claimed compounds comprising the 3-aza-bicyclo[3.2.1]octane core, and bioactive compounds are routinely formulated as pharmaceutical compositions for administration in therapeutic methods. The person of ordinary skill in the art would have expected that the compounds could be formulated with routinely used, pharmaceutically acceptable excipients absent evidence to the contrary.

Claims 22-25, 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cini et al (Eur J of Org Chem, March 2002, 873-880).

Cini et al. teach compounds within the scope of the scope of the instant genus of compounds comprising the 3-aza-bicyclo[3.2.1]octane core, as well as specific compounds defined in the instant claim 25. For example, Cini et al. teach compounds 17-20 of the instant claim 25 where X, Y, Z are O, R1, R4, R5 are H, R2 is C1- C8 hydroxyalkyl, R3 is C1arylalkyl, and R6 is (R)-C(O)OR, wherein R is C1 alkyl (see compounds 16 and 20 of page 875). The reference also teach compounds 13-16 of the instant claim 25 where X, Y, Z are O, R1, R4, R5 are H, R2 is C1-C8alkyloxyaryl, R3 is C1arylalkyl, and R6 is (R)-C(O)OR, wherein R is C1 alkyl (see compound 8, page 874). The reference teach the compounds in solvents and as intermediates in the synthesis of

compounds (BTS) that are transformed into a novel, conformationally constrained α-amino acid that may find its application in peptidomimetic synthesis. The reference teach the composition of the compounds as the compounds are in solvents such as ethanol (p 875, para 2, line 5).

Cini et al. do not teach preparation of pharmaceutical compositions comprising the herein-claimed compounds comprising the 3-aza-bicyclo[3.2.1]octane core. The reference does not explicitly teach the stereoisomers of the compounds of the claimed invention.

The herein-claimed stereoisomers of the compounds disclosed by Cini et al. are prima facie obvious, particularly considering that Cini et al. teach a general strategy for preparing all of the possible stereoisomers. Because Cini et al. suggest the utility of the herein-claimed compounds comprising the 3-aza-bicyclo[3.2.1]octane core to be a precursor of the compounds that may find its application in peptidomimetic synthesis, it would have been obvious to the person of ordinary skill in the art to formulate the compounds with pharmaceutically acceptable excipients to arrive at the instantly claimed inventions.

The person of ordinary skill in the art would have been motivated to formulate the compounds of Cini et al. with pharmaceutically acceptable excipients as a pharmaceutical composition because Cini et al. teach that the compounds as precursors of compounds with pharmaceutical utility, and bioactive compounds are routinely formulated as pharmaceutical compositions for administration in therapeutic methods. The person of ordinary skill in the art would have expected that the

compounds could be formulated with routinely used, pharmaceutically acceptable excipients absent evidence to the contrary.

Response to Arguments

Applicants' arguments regarding the rejection of claims 22-26, 42 under 35 U.S.C. 103(a) as being unpatentable over Guarna et al. (Applicant-cited reference on IDS: Guarna et al. J. *Org.Chem.* 1999, *64,* 7347-7364) and the rejection of claims 22-26, 42 under 35 U.S.C. 103(a) as being unpatentable over Cini et al (Eur J of Org Chem, March 2002, 873-880).have been fully considered and found not persuasive. Applicants' argue that "[I]f the prior art merely discloses compounds as intermediates in the production of a final product, one of ordinary skill in the art would not ordinarily stop the reference synthesis and investigate the intermediate compounds with an expectation of arriving at claimed compounds which have different uses." In response, the Applicants' are right that the compounds in the composition claimed are pharmaceutically active and not merely synthetic intermediates. Gurana in the prior art teaches the BTAa(O) compounds, (some of the compounds that are instantly claimed) as corresponding amide precursors of BTAs (dipeptide isoteres). The reference teaches the compounds in the instantly claimed invention as amide precursors and not as intermediates. Furthermore, the reference teaches them as amide precursors of BTAs (dipeptide isoteres), compounds that can replace one or more amino acids in a bioactive peptide leading to modified structures possibly displaying more favorable pharmacological properties than the prototype. Because Guarna et al. suggest the pharmaceutical utility of the herein-claimed compounds comprising the 3-aza-bicyclo

[3.2.1]octane core, it would have been obvious to the person of ordinary skill in the art to formulate the compounds with pharmaceutically acceptable excipients to arrive at the instantly claimed inventions.

Applicants' argue that Guarna fails to teach or suggest a specific pharmaceutical utility for any of the disclosed compounds. As stated earlier in the rejection Guarna teach compounds within the scope of the instant genus of compounds comprising the 3-aza-bicyclo[3.2.1]octane core, as well as specific compounds defined in the instant claim 25. The reference teach the utility of BTAa(O) compounds as the precursor of dipeptide isoteres that can replace one or one or more amino acids in a bioactive peptide leading to modified structures possibly displaying more favorable pharmacological properties than the prototype. Hence the reference teach the usefulness of the compounds in preparation of dipeptide isoteres and a person of ordinary skill in the art would have expected that the compounds could be formulated with routinely used, pharmaceutically acceptable excipients absent evidence to the contrary.

Applicants' argue that Cini et al. fails to teach or suggest a specific pharmaceutical utility or pharmaceutical composition any of the 2-oxo forms of BTAa or the BTAa compounds. In response, as stated above, the person of ordinary skill in the art would have been motivated to formulate the compounds of Cini et al. with pharmaceutically acceptable excipients as a pharmaceutical composition because Cini et al. teach that the compounds as precursors of compounds with pharmaceutical utility, and bioactive compounds are routinely formulated as pharmaceutical compositions for

administration in therapeutic methods. The person of ordinary skill in the art would have expected that the compounds could be formulated with routinely used, pharmaceutically acceptable excipients absent evidence to the contrary. Applicants' further argue that compound 8 of Cini et al. in ethanol does not teach or suggest the claimed pharmaceutical composition and the ethanol in synthetic reactions are typically not performed in such solvents. In response, Cini et al. teaches a composition of a 2-oxo compound in ethanol and ethanol is one of the pharmaceutically acceptable excipient. It would have been obvious to one of ordinary skilled in the art to routinely formulate bioactive compounds in pharmaceutically acceptable excipients with quality or purity suitable for pharmaceutical use because Cini et al. teach that the compounds as precursors of compounds with pharmaceutical utility.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the modified rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617